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ORIGINAL RESEARCH

Social Isolation and Incident Heart Failure Hospitalization in Older Women: Women's Health Initiative Study Findings

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BACKGROUND: The association of social isolation or lack of social network ties in older adults is unknown. This knowledge gap is important since the risk of heart failure (HF) and social isolation increase with age. The study examines whether social isolation is associated with incident HF in older women, and examines depressive symptoms as a potential mediator and age and race and ethnicity as effect modifiers.

METHODS AND RESULTS: This study included 44 174 postmenopausal women of diverse race and ethnicity from the WHI (Women's Health Initiative) study who underwent annual assessment for HF adjudication from baseline enrollment (1993–1998) through 2018. We conducted a mediation analysis to examine depressive symptoms as a potential mediator and further examined effect modification by age and race and ethnicity. Incident HF requiring hospitalization was the main outcome. Social isolation was a composite variable based on marital/partner status, religious ties, and community ties. Depressive symptoms were assessed using CES-D (Center for Epidemiology Studies-Depression). Over a median follow-up of 15.0 years, we analyzed data from 36 457 women, and 2364 (6.5%) incident HF cases occurred; 2510 (6.9%) participants were socially isolated. In multivariable analyses adjusted for sociodemographic, behavioral, clinical, and general health/functioning; socially isolated women had a higher risk of incident HF than nonisolated women (HR, 1.23; 95% CI, 1.08–1.41). Adding depressive symptoms in the model did not change this association (HR, 1.22; 95% CI, 1.07–1.40). Neither race and ethnicity nor age moderated the association between social isolation and incident HF.

CONCLUSIONS: Socially isolated older women are at increased risk for developing HF, independent of traditional HF risk factors.

REGISTRATION: URL: http://www.clinicaltrials.gov; Unique identifier: NCT00000611.

Key Words: heart failure ■ older adults ■ social isolation ■ women

Social isolation—defined as objective lack of or disengagement from social ties, institutional connections, or community participation[1]—is strongly associated with all-cause and cardiovascular mortality, particularly in older adults.[2,3] Few prospective studies have examined the role of social isolation in heart failure (HF) incidence.[4] Using data from the ARIC

(Atherosclerosis Risk in Communities) study, Cené and colleagues demonstrated that social isolation is a predictor of incident HF among middle-aged adults (mean age of 57 years) at study enrollment.[5] However, it is unclear whether social isolation predicts incident HF in older adults and whether the association is stronger with increasing age. Like HF prevalence, the risk

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Nonstandard Abbreviations and Acronyms

WHI   Women's Health Initiative

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of social isolation also increases with age as network disruption occurs because of life course factors such as retirement, bereavement, declining health status, or physical disability. A recent poll of a nationally representative sample of over 2000 adults aged 50 to 80 years found that 27% of respondents reported being socially isolated.[6] Strong evidence shows a nearly 2-fold higher cardiovascular risk among those who are socially isolated.[7,8]

There are several pathways by which social isolation might influence HF risk.[9,10] Social isolation is considered a stressor that has several effects. It can induce a negative psychological state which can increase neuroendocrine responses; reduce levels of protective hormones, leading to adverse effects on heart rate, blood pressure, and repair of blood vessel walls; downregulate the immune system; and suppress immune function. Because of their lack of social networks or support, socially isolated individuals may suffer more stress than others. They may also be more likely to become depressed and disengage from participating in health-promoting activities. Strong evidence suggests that lack of social integration is associated with depression.[11,12] Few studies have sought to examine potential mediating pathways between social isolation and incident HF.[2] Our study objectives were to: (1) examine whether socially isolated participants in the WHI (Women's Health Initiative) study are at higher risk for developing HF compared with those who are not socially isolated, (2) assess whether an observed association is modified by age and race and ethnicity, and (3) examine depression as a mediator of any observed association between HF and social isolation.

METHODS

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure.[13]

Data Source

The WHI is a US study funded by the National Heart, Lung, and Blood Institute. Postmenopausal women were followed for >20 years, being evaluated for cardiovascular disease, cancer, and osteoporosis.[14–16] The original WHI sample at 40 clinical centers across the United States from 1993 to 1998 included 161 809 postmenopausal women aged 50 to 79 years, making it one of the largest studies of women. Participants were enrolled in either ≥1 randomized clinical trials or an observational study. They were then followed at least annually to track vital status and medical outcomes until study closeout (October 2004–March 2005).[17] After closeout, all participants were invited to enroll in 2 extension studies (2010–2015, 2015–2020) to continue tracking their health status. The study included self-reported medical information collected through interviews and surveys, anthropometric measurements by WHI personnel, and review of medical records for outcomes determination. To ensure uniform data collection; standardized written protocols, centralized training of staff, and quality assurance visits by the Clinical Coordinating Center were used.

Study Population

Our analytic sample included a subcohort of the original WHI population, selected to participate in a study on the epidemiology of HF in postmenopausal women. This sample included 44 174 postmenopausal women of diverse race and ethnicity, all who underwent annual assessment for HF adjudication from baseline enrollment (1993–1998) through 2018. It also included all participants who were randomized to the WHI hormone therapy trial (n=27 347) as well as an oversampling of minorities comprising all non-hormone trial Black (n=11 880) and Hispanic (n=4947)

women. We excluded women with a diagnosis of HF at baseline (n=430) and those missing data on variables used to define social isolation (n=3210) and other key covariates (n=3768). The final analytic sample included 36 457 participants. (Figure 1) The study was approved by the Human Subjects Review Committees at each
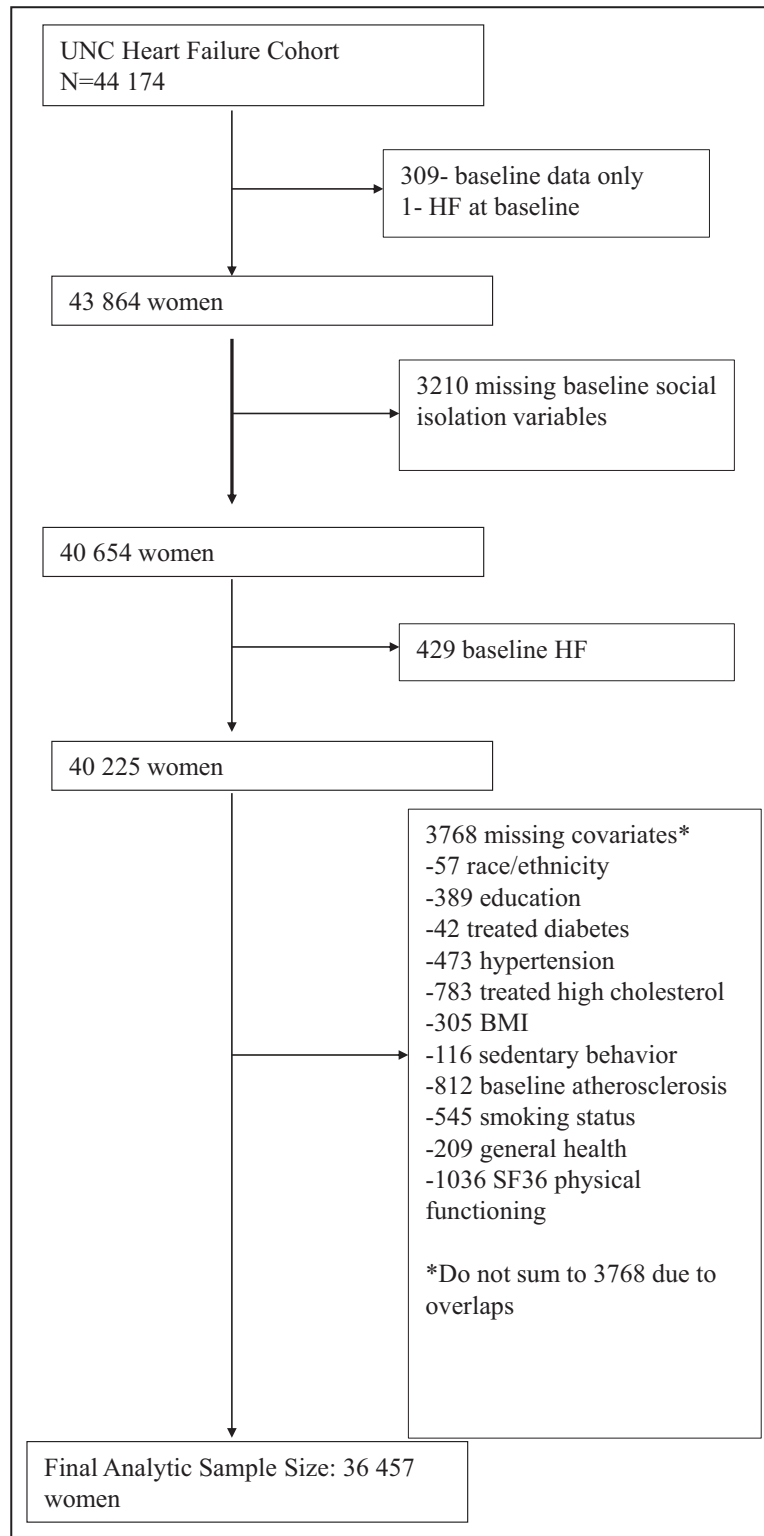

Figure 1. Analytic sample.
BMI indicates body mass index; and HF, heart failure; SF36, Short Form 36.

WHI participating institution, and all participants provided written informed consent.

Outcome of Interest

Participants were followed from study enrollment until incident HF requiring hospitalization. Adjudication for HF hospitalization was based upon annual review of medical records and self-report of hospitalizations. WHI defined incident HF hospitalization as "definite or probable," according to symptoms, physical exam, clinical data, and medical therapy provided during hospitalizations as previously reported.[18]

Exposure of Interest

Using an adapted version of the Berkman–Syme social network index, social isolation was broadly defined as a relative lack of social network ties[19,20] and was assessed at 4 time periods. This index weights 3 different types of participant-reported social network ties: intimate contact (spousal ties), religious ties, and community/group membership. To assess marital status, we asked, "Are you currently married or in an intimate relationship with at least one person?" (yes or no). Specific wording for the questions on religious ties was as follows: "How often have you gone to a religious service or to a church in the past month?" and "How often have you gone to the meetings of clubs, lodges, or parent groups in the past month?" Response options for religious and community participation questions were on a 1 to 6 scale with 1 representing not at all and 6 representing every day. Women who indicated that they were not married/partnered, had no religious ties, and no community ties were considered socially isolated. Our analysis compares women who were socially isolated versus not socially isolated. Unlike the original Berkman–Syme social network index, we did not include number and frequency of contacts with children, close friends, and close relatives in our definition of social isolation because this variable was not assessed in WHI at baseline.

We constructed a composite social isolation variable that considered marital status, religious ties, and community/group membership. In sensitivity analyses, we considered "living alone" as a proxy for social isolation.

Covariates

Guided by the Berkman–Glass conceptual model of social networks on health outcomes,[21] we created a causal diagram to identify potential confounders of the association between social isolation and incident HF hospitalization.[22] We grouped covariates into 3 groups of factors: demographic, health status, and lifestyle/behavioral and clinical. Demographic factors included: age (continuous); race and ethnicity (White, Black, Hispanic, Asian/Pacific Islander, American Indian/Alaskan Native, Other/Multiple), education, and WHI enrollment (clinical trial versus observational study). Health status factors included: self-rated overall health (first item of Short-Form 12; 5-point Likert scale- Excellent to Poor)[23,24] and physical functioning. Lifestyle/behavioral and clinical factors included: sedentary behavior (<500 metabolic equivalent of task minute/week)[25]; body mass index (continuous and categorical body mass index ≥30 versus <30); smoking—defined as prior hospitalization for myocardial infarction, prior coronary artery bypass graft surgery, prior percutaneous coronary intervention (coronary artery bypass graft, percutaneous transluminal coronary angioplasty), history of carotid artery disease, stroke/transient ischemic attack or peripheral vascular disease; history of treated diabetes mellitus (yes/no); history of treated high cholesterol (yes/no); and hypertension status (never hypertensive, currently treated, currently untreated). We also included incident myocardial infarction as a time-dependent covariate.

Mediator

We hypothesized that depressive symptoms may mediate the association between social isolation and incident HF. Depressive symptoms were measured at 4 different time periods using the 8-item Burnham short version of the CES-D (Center for Epidemiologic Studies-Depression).[26] Responses for each item were weighted according to the Burnham algorithm with a final range from 0 to 1—higher scores indicate greater likelihood of depression. Scores >0.06 are indicative of significant depressive symptoms, and scores ≤0.06 are indicative of no/minimal depressive symptoms.

Effect Moderator Variables

We examined age at baseline and race and ethnicity as potential modifiers of the association between social isolation and incident HF hospitalization.

Statistical Analysis

Women's characteristics overall and by baseline social isolation status were summarized using means (SD) for continuous variables and frequencies (percentages) for categorical variables. For continuous variables and categorical variables, we used Student t-test and Chi-square tests to examine differences between social isolation groups. In 3 models, after sequential adjustment for potential confounding variables, we used Cox proportional hazards regression with time-dependent covariates (social isolation composite and its individual indicators, depressive symptoms, and incident myocardial infarction) to estimate hazard ratios (HR) and

95% CI for the association between social isolation and time to incident HF hospitalization. In the minimally adjusted model (model 0), we adjusted for age, race, education level, study arm (clinical trial versus observational study), and hormone therapy arm. In the first fully adjusted model (Model 1), we included covariates in Model 0, as well as treated diabetes, hypertension status, treated high cholesterol, body mass index, sedentary behavior, prevalent cardiovascular disease (CVD) and incident myocardial infarction, smoking, general health status, and physical functioning. In the second fully adjusted model (Model 2), we added depressive symptoms to the covariates in Model 1. When fitting models, for race and ethnicity, we combined American Indian/Alaskan Native and other/Mixed as 1 category.

We used an ad hoc approach to examine the role of depressive symptoms as a potential mediator. First, we used depressive symptoms as predictor in Models 0 and 1. We then fit a Generalized Estimating Equations model to analyze the associations between social isolation and depressive symptoms, considering the within-subject correlations. Model 3 was used to evaluate the mediating impact of depressive symptoms on social isolation.

We further analyzed each social isolation indicator separately. Based on Model 1, we examined interactions by race and ethnicity and age. Evidence of interaction was determined based on a statistically significant P value for the interaction term at the $P<0.05$ level.

We conducted sensitivity analysis to examine how a different composite definition of social isolation (adding "live alone") affected our results. We also performed survival analyses with CVD death as competing risk. All statistical procedures were performed with the use of SAS version 9.4 (SAS Institute Inc, Cary, NC). All tests were 2-sided with significance level of $P<0.05$.

RESULTS

From 1993 to 2018 (median follow-up 15.0 years), we had 36 457 participants in the analytic sample, and 2364 (6.5%) incident HF cases occurred. Mean age of sample was 62.6 years; 32.8% of sample was Black women, and 14% were Latina. In our sample, 2510 (6.9%) participants were socially isolated. Sociodemographic and clinical characteristics at baseline (Table 1) showed statistically significant differences between socially isolated and non-isolated women. For those in the socially isolated group, the percentage of women with a CES-D score of >0.06 (indicative of a significant depressive symptoms) was higher (19% versus 12%; $P<0.001$).

Table 2 lists the unadjusted and adjusted HR of HF incidence based on social isolation status. The minimally adjusted risk of HF was 56% higher in women who were socially isolated (Model 0: HR, 1.56%; 95%

CI, 1.37–1.78). Socially isolated women had significantly greater risk of developing HF in the fully adjusted model (Model 1: HR, 1.23; 95% CI, 1.08–1.41). Figure 2 shows the Kaplan–Meier plot of time to incident HF hospitalization by baseline social isolation status. In the ad hoc mediation analysis, Generalized Estimating Equation model results indicated that social isolation increased risk of depressive symptoms (regression coefficient, 0.27; 95% CI, 0.20–0.34; $P<0.001$). Depressive symptoms were independently associated with incident HF (Model 0: HR, 1.21; 95% CI, 1.06–1.38; $P=0.005$) in the minimally adjusted model; however, the association was diminished in both fully adjusted models (Model 1: HR, 0.93; 95% CI, 0.81–1.06; $P=0.26$; Model 2: HR, 0.92; 95% CI, 0.80–1.05; $P=0.23$). After additionally adjusting for depressive symptoms, the association between social isolation and incident HF remained significant (Model 2: HR, 1.22; 95% CI, 1.07–1.40, $P=0.003$), with a similar HR, indicating that depressive symptoms might not mediate the association between social isolation and incident HF risk. Effect modification by race and ethnicity or baseline age of the association between social isolation and incident HF was not statistically significant based on the tests of interactions (Table 2). Figure 3 summarizes the results of our findings according to our conceptual model.

Table 3 provides the HRs for each covariate in multivariable Model 1. The following covariates were associated with a significantly increased risk of incident HF hospitalization: age, treated diabetes, obesity, prevalent CVD, incident myocardial infarction, and poor general self-reported health. A significantly decreased risk of incident HF was associated with non-White race and ethnicity, hypertensive status (never hypertensive or controlled hypertension), and never or past smoking. Adjusting for depressive symptoms did not alter the association between these covariates and risk of incident HF hospitalization (data not shown).

Survival analyses using CVD death as competing risk against HF did not change the results materially (data not shown).

Notably, "living alone", which is often used clinically as a proxy for social isolation, was not associated with time to incident HF hospitalization (Model 2: HR, 0.97; 95% CI, 0.89–1.06, $P=0.52$). Living alone was highly correlated with marital/partnered status (data not shown); therefore, we did not include it in the social isolation composite.

DISCUSSION

Our study yielded 3 main findings. First, social isolation (defined by a lack of marital/partnered, religious, and community ties) was significantly associated with incident HF hospitalization, the risk being, on average,

Table 1. Participant Characteristics at Baseline

	Overall, n (%)	Not socially isolated, n (%)	Socially isolated, n (%)	*P* value
Total	36 457	33 974	2510	
Age (y), mean (SD)	62.6 (7.2)	62.6 (7.2)	62.6 (7.3)	0.73
Race and ethnicity				
American Indian/Alaskan Native	107 (0.3)	94 (0.3)	13 (0.5)	<0.001
Asian/Pacific Islander	481 (1.3)	434 (1.3)	47 (1.9)	
Black	11 960 (32.8)	11 324 (33.4)	636 (25.3)	
Hispanic/Latino	5058 (13.9)	4760 (14.0)	298 (11.9)	
White	18 566 (50.9)	17 064 (50.3)	1502 (59.8)	
Other/multiple	285 (0.8)	271 (0.8)	14 (0.6)	
Education				
Less than high school	3456 (9.5)	3199 (9.4)	257 (10.2)	0.005
High school/vocational training	11 111 (30.5)	10 365 (30.5)	746 (29.7)	
Some college/associate degree	10 157 (27.9)	9397 (27.7)	760 (30.3)	
College/graduate	11 733 (32.2)	10 986 (32.4)	747 (29.8)	
Observational study				
No	27 231 (74.7)	25 255 (74.4)	1976 (78.7)	<0.001
Yes	9226 (25.3)	8692 (25.6)	534 (21.3)	
Hormone therapy arm				<0.001
Not in hormone therapy trial	13 704 (37.6)	12 978 (38.2)	726 (28.9)	
CEE alone control	4386 (12.0)	4033 (11.9)	353 (14.1)	
CEE alone intervention	4404 (12.1)	4046 (11.9)	358 (14.3)	
CEE+MPA control	7053 (19.4)	6483 (19.1)	570 (22.7)	
CEE+MPA intervention	6910 (18.9)	6407 (18.9)	503 (20.0)	
Depressive symptom				
No	30 933 (87.3)	28 976 (87.8)	1957 (80.7)	<0.001
Yes	4490 (12.7)	4023 (12.2)	467 (19.3)	
Smoking status				
Never smoked	18 676 (51.2)	17 790 (52.4)	886 (35.3)	<0.001
Past smoker	14 095 (38.7)	13 020 (38.4)	1075 (42.8)	
Current smoker	3686 (10.1)	3137 (9.2)	549 (21.9)	
BMI (kg/m^2), mean (SD)	29.6 (6.3)	29.6 (6.2)	29.7 (6.6)	0.30
Obesity				
No	21 526 (59.0)	20 062 (59.1)	1464 (58.3)	0.45
Yes	14 931 (41.0)	13 885 (40.9)	1046 (41.7)	
High cholesterol requiring pills				
No	31 315 (85.9)	29 145 (85.9)	2170 (86.5)	0.40
Yes	5142 (14.1)	4802 (14.1)	340 (13.5)	
Hypertension				
Never hypertensive	22 298 (61.2)	20 704 (61.0)	1594 (63.5)	<0.001
Current/treated	3294 (9.0)	3023 (8.9)	271 (10.8)	
Current/untreated	10 865 (29.8)	10 220 (30.1)	645 (25.7)	
Treated diabetes				
No	33 783 (92.7)	31 467 (92.7)	2316 (92.3)	0.43
Yes	2674 (7.3)	2480 (7.3)	194 (7.7)	
Sedentary behavior				
No	15 129 (41.5)	14 277 (42.1)	852 (33.9)	<0.001
Yes	21 328 (58.5)	19 670 (57.9)	1658 (66.1)	

(Continued)

Table 1.   Continued

	Overall, n (%)	Not socially isolated, n (%)	Socially isolated, n (%)	P value
Prevalent CVD				
No	33 788 (92.7)	31 480 (92.7)	2308 (92.0)	0.15
Yes	2669 (7.3)	2467 (7.3)	202 (8.0)	
Incident MI				
No	34 928 (95.8)	32 549 (95.9)	2379 (94.8)	0.008
Yes	1529 (4.2)	1398 (4.1)	131 (5.2)	
General health				
Excellent	4865 (13.3)	4545 (13.4)	320 (12.7)	<0.001
Very good	13 582 (37.3)	12 700 (37.4)	882 (35.1)	
Good	13 549 (37.2)	12 662 (37.3)	887 (35.3)	
Fair	4095 (11.2)	3726 (11.0)	369 (14.7)	
Poor	366 (1.0)	314 (0.9)	52 (2.1)	
SF36—physical functioning, mean (SD)	79.0 (21.5)	79.2 (21.3)	76.2 (23.5)	<0.001

BMI indicates body mass index; CEE, combined equine estrogens; CVD, cardiovascular disease; MI, myocardial infarction; and MPA, medroxyprogesterone acetate; SF36, Short Form 36.

23% higher in socially isolated versus non-isolated older women. Second, and contrary to our hypothesis, depressive symptoms did not mediate the association between social isolation and incident HF hospitalization. Third, the association does not differ by race and ethnicity or age.

Few population-based studies have examined the association between social isolation (or social network characteristics more broadly) and incident HF.[4,5] Other studies have also documented strong associations of social isolation with hospital readmission in patients with HF.[27] Our findings confirm previous work conducted in the ARIC (Atherosclerosis Risk in Communities) cohort study, which found that the risk of developing incident HF (defined as incident HF hospitalization or death) was 21% higher in middle-aged men and women (mean [SD] age of 56.9 [SD, 5.7] years) with moderate/high social isolation risk compared with

those with low social isolation.[5] We extend this literature by documenting this independent association in older women (mean [SD] age of 62.6 [SD, 7.2] years) using a different measure of social isolation. On the contrary, Rod and colleagues did not find an association between social network characteristics and incident HF hospitalization.[4] This may be because of differences in study population (Danish sample) and social network measurement (examined living alone and regular contact with family and friends as their social network indicators).

A 2016 systematic review and meta-analysis examining the prospective association between social isolation or loneliness found that poor social relationships were associated with a 29% increased risk of incident coronary heart disease[28]—a major predisposing factor for HF. Since our social isolation definition did not include an assessment of family and friendship ties, it is

Table 2.   Association Between Incident HF Hospitalization and Social Isolation (Total Number of Observations: 36 457; Total Number of Events: 2364)

Predictor	Model 0*		Model 1†		Model 2‡		Interaction P value§	Interaction P value‖
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value		
Social isolation¶	1.56 (1.37–1.78)	<0.001	1.23 (1.08–1.41)	0.002	1.22 (1.07–1.40)	0.003	0.29	0.94
Not married or intimate	1.25 (1.15–1.35)	<0.001	1.11 (1.02–1.20)	0.020	1.10 (1.01–1.20)	0.024	0.21	0.16
No religion tie#	1.19 (1.09–1.30)	<0.001	1.06 (0.97–1.16)	0.22	1.06 (0.97–1.16)	0.23	0.50	0.92
No community tie#	1.15 (1.06–1.25)	<0.001	1.01 (0.93–1.10)	0.75	1.01 (0.93–1.10)	0.77	0.48	0.47
Live alone	1.00 (0.92–1.09)	0.98	0.97 (0.89–1.06)	0.11	0.97 (0.89–1.06)	0.52	0.14	0.27

*Model 0: adjusted for age, race, education, study arm (clinical trial vs observational study), hormone therapy arm.

†Model 1: Adjusted for age, race, education, study arm (clinical trial vs observational study), hormone therapy arm, treated diabetes, hypertension status, treated high cholesterol, obesity, sedentary behavior, prevalent cardiovascular disease and incident myocardial infarction, smoking, self-rated health status, and physical functioning.

‡Model 2: model I plus most recent depressive symptoms as time-varying covariate.

§Interaction between race and ethnicity and predictor for Model 1.

‖Interaction between baseline age and predictor for Model 1.

¶The sum of not married, no religion tie, and no community tie was calculated. If the sum is 3, then social isolation="Yes".
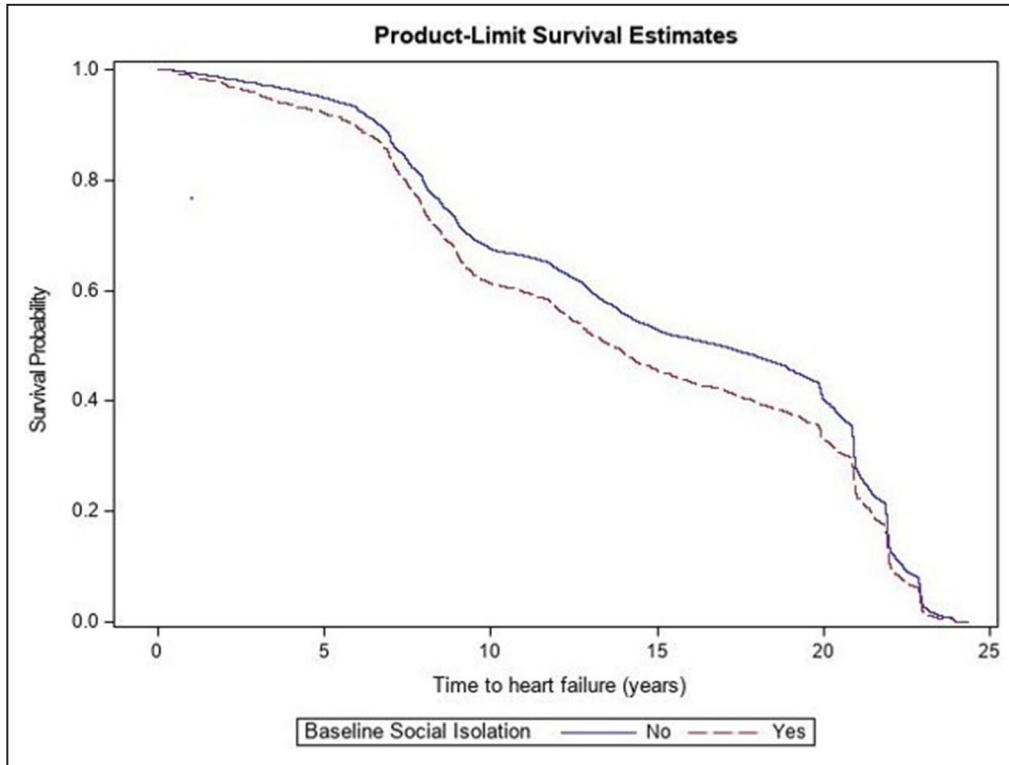
#Defined as not at all in the past month.

Figure 2. Kaplan–Meier product limit estimate of the cumulative incidence of heart failure hospitalization over time by social isolation status (socially isolated vs nonisolated) at baseline.

possible that the strength of our association is overestimated. However, our previous work in the ARIC study used a measure of social isolation which did include friends and family ties and demonstrated a similar effect size to the current study.[5] Prior literature has noted significant changes in network size and composition

with age, with some studies showing that networks shrink, while others show that the total network size remains stable as the number of close relatives increases and the number of friends decreases.[29] Although HF disproportionately affects underrepresented racial and ethnic women,[30,31] and some data demonstrate that
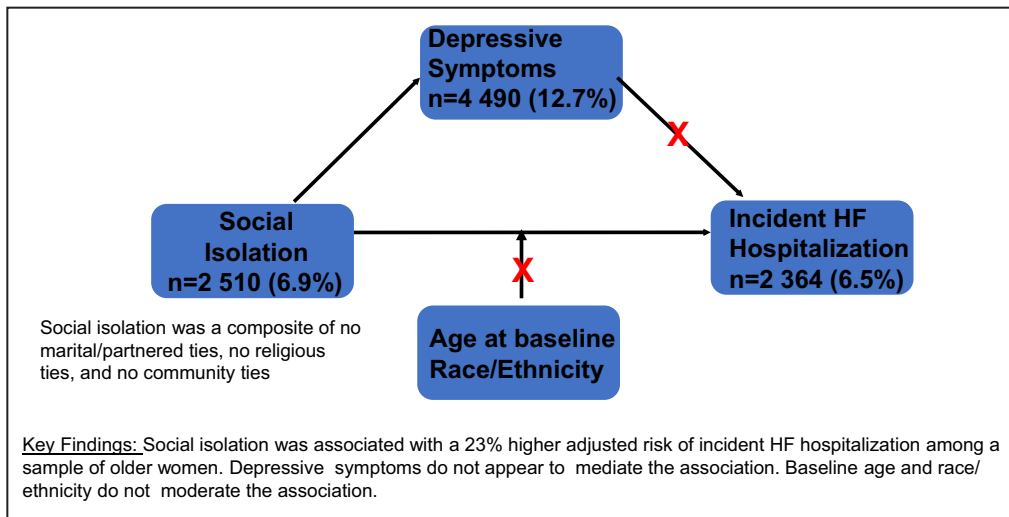

Figure 3. Conceptual model of direct, mediating, and moderating effects of social isolation on incident HF hospitalization in 36 457 older women (mean age, 62 years) from the WHI (Women's Health Initiative) study over mean follow-up of 15 years.

Table 3. HRs of Incidence HF Hospitalization of Covariates in Model 1

Covariates	HR (95% CI)	P value
Baseline age per year	1.09 (1.09–1.10)	<0.001
Race and ethnicity (vs White)		<0.001
Asian/Pacific Islander	0.71 (0.46–1.11)	
Black	0.78 (0.66–0.91)	
Hispanic/Latino	0.61 (0.49–0.76)	
Other	0.97 (0.67–1.40)	
Education (vs college/graduate)		0.32
Less than high school	1.08 (0.92–1.27)	
High school/vocational training	1.19 (0.99–1.22)	
Some college/associate degree	1.08 (0.97–1.20)	
Treated diabetes	2.35 (2.08–2.64)	<0.001
Hypertension		<0.001
Never hypertensive	0.58 (0.53–0.64)	
Controlled hypertension	0.70 (0.60–0.81)	
Treated high cholesterol	0.96 (0.86–1.07)	0.43
Obesity (BMI ≥30)	1.34 (1.23–1.47)	<0.001
Sedentary behavior	1.09 (1.00–1.19)	0.06
Smoking status (vs current smoker)		<0.001
Never smoked	0.45 (0.39–0.51)	
Past smoker	0.55 (0.48–0.63)	
Prevalent CVD	1.82 (1.62–2.05)	<0.001
Incident MI	2.90 (2.53–3.33)	<0.001
General health (vs excellent)		0.002
Very good	1.11 (0.95–1.29)	
Good	1.15 (0.98–1.34)	
Fair	1.44 (1.19–1.76)	
Poor	1.39 (0.94–2.05)	
Physical functioning per 1 unit increase	0.991 (0.989–0.993)	<0.001
Hormone therapy arm (vs not in hormone therapy trial)		0.002
CEE alone control	1.41 (1.14–1.73)	
CEE alone intervention	1.36 (1.10–1.68)	
CEE+MPA control	1.18 (0.95–1.46)	
CEE+MPA intervention	1.24 (1.00–1.53)	

BMI indicates body mass index; CEE, combined equine estrogens; CVD, cardiovascular disease; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; and MPA, medroxyprogesterone acetate.

social network size and social isolation differ by race and ethnicity,[32] we did not find evidence that the association between social isolation and HF risk differed by race and ethnicity.

Contrary to our hypothesis, we did not find evidence that depressive symptoms mediated the effect of social isolation on incident HF. Among the few studies that have examined the association between depressive symptoms and incident HF, including some focused on older populations, results have been mixed.[33–36] It is possible that the association is only evident among subgroups, such as individuals with poor health at baseline.[34]

The mechanisms through which social isolation influences cardiovascular risk (including HF) are unknown but are hypothesized to include neuroendocrine pathways, health behaviors, and physiologic pathways such as inflammation.[2,9,37] Social isolation may predispose individuals to chronic psychosocial distress and toxic biological stress response. This stress response causes sympathetic activation which can facilitate pathogenic processes involved in coronary heart disease and ultimately HF. Identification of mediators is crucial so that clinicians and researchers can better assess risk of developing HF and subsequently intervene before HF develops or worsens. Cené and colleagues previously demonstrated that vital exhaustion, an aspect of functional status, which shares common symptomatology with depression (fatigue, irritability, and feelings of demoralization), mediated the association between social isolation and incident HF in middle-aged adults.[5]

Our study had several notable limitations. First, our definition of social isolation did not include frequency of contact with family and friends. This type of social interaction is sometimes used in composite definitions of social isolation and is a known correlate of social isolation.[38] Second, we used HF hospital admissions as a proxy measure of heart failure incidence. However, HF hospitalization was an adjudicated outcome and the specificity for accurately identifying individuals with clinical heart failure is likely high. Third, as with all observational studies, there is a potential for residual confounding because of unmeasured variables, such as loneliness (perceived isolation),[7] other aspects of psychosocial distress (eg, anxiety, stress), or clinical conditions that could impede social connections (eg, hearing or vision loss, limited mobility). Finally, WHI solely includes older women; therefore, results may not be generalizable to men or younger women.

Despite these limitations, our study has several strengths. Notably, we addressed an important and timely research question for older adults and women's health.[4] A recent publication highlights the need for increased attention to the pathophysiology of heart disease in women and emphasizes the importance of conducting sex-specific examinations.[39] Second, we leveraged the strengths of the WHI study, including population-based sampling, large sample size, and extended follow-up time. The large sample size allowed for greater accuracy of results and the ability to simultaneously adjust for confounders. Finally, our analysis remained sensitive to different definitions of social isolation, thus bolstering the validity of our findings.

Identifying and addressing health implications of social isolation is important from a clinical and public health standpoint. There is increasing interest in

social determinants of health (including social isolation) as predictors of health and well-being. The National Academy of Medicine has recommended routine assessment for social isolation in healthcare settings[40] and they endorse a 5-item measure of social isolation (based on the same measure we used) that queries the frequency of talking to or getting together with family or friends in a typical week, attending church or religious services, attending meetings of clubs or organizations, and marital status. Healthcare providers should consider screening for social isolation in older adults at risk for HF in addition to traditional HF risk factors and using extant evidence to guide intervention strategies to mitigate social isolation, including referrals to community resources.[41,42] Future research should seek to identify mediating pathways through which social isolation influences the development of HF and other clinical conditions.

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